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Screening and the epidemic of thyroid cancer in China: An analysis of national representative inpatient and commercial insurance databases

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Abstract

Reasons behind the rapid increase of thyroid cancer (TC) in China are uncertain. We assessed the burden of TC and the role of access to screening and salt iodization. We analyzed two national databases in China: Hospital Quality Monitoring System (HQMS) and China Reinsurance Company (CRC) database. HQMS covered 1037 (44.3%) Class 3 hospitals and 76 263 617 Class 3 hospital inpatients in 2013 to 2017 and CRC covered 93 123 018 clients in 2000 to 2016. The proportion of TC inpatients among inpatients in HQMS and TC incidence in critical illness insurance buyers were used to evaluate the association with screening and iodine status. Between 2013 and 2017, the proportion of TC patients in HQMS with urban employee medical insurance and good access to screening increased sharply while there was little change among those with the other two forms of medical insurance. Across provinces, the proportion of TC inpatients in HQMS was positively correlated with per capita disposable income but not with median urinary iodine. Similar findings were observed in the CRC database. In 2017, approximately 1000 individuals were overdiagnosed with TC daily. We conservatively forecast that 5.1 million healthy individuals would become TC patients unnecessarily between 2019 and 2030. Our findings suggested the epidemic of TC in China was substantially underestimated. It was associated with screening but not with salt iodization.

KEYWORDS

epidemic, incidence, salt iodization, screening, thyroid cancer

Abbreviations: APC, annual percentage change; CI, confidence interval; CII, critical illness insurance; CRC, China Reinsurance Company; HQMS, Hospital Quality Monitoring System; ICD-10, International Classification of Diseases-10; IDDs, iodine deficiency disorders; IQR, interquartile range; MUI, median urinary iodine; PCDI, per capita disposable income; PTC, papillary thyroid cancer; RMI, rural medical insurance; TC, thyroid cancer; UEMI, urban employee medical insurance; URMI, urban resident medical insurance.

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1 | INTRODUCTION

The incidence of thyroid cancer (TC) had increased rapidly worldwide in recent decades.[1] Since 1975, the incidence in the United States had increased from 4.9/100 000 to 14.3/100 000 in 2009.[2] In South Korea, the incidence of TC in 2011 was 15 times that observed in 1993 though mortality rates had remained unchanged.[3] TC had also become the fastest growing malignancy in China, with the annual percentage change (APC) of the incidence in women rising from 4.9% in 2000 to 2003 to 20.1% in 2003 to 2011.[4] According to a national report published by National Cancer Center of China, the estimated incidence in 2014 was 12.40/100 000.[5]

Screening leads to increased detection of asymptomatic TC lesions.[6-8] Thyroid nodules were found in 68% of asymptomatic people by high-resolution ultrasound examination in Germany.[9] About 7% to 15% of thyroid nodules were malignant.[10] A national screening program was initiated for cancer and other common diseases in South Korea in 1999, and the incidence of TC rapidly increased since then.[3] However, a sharp fall was observed since a physician coalition advocated the stopping of screening in 2014.[11] In the United States, high-income counties experienced more rapid increases in incidence than low-income counties since 1975. People with higher incomes were exposed to increased health check intensity.[7] In the past decade, the government of China initiated reforms to achieve universal access to health care. From 2003 to 2011, social medical insurance coverage increased from 29.7% to 95.7%.[12] There are three types of insurance: rural medical insurance (RMI), urban resident medical insurance (URMI) and urban employee medical insurance (UEMI). The odds of regular health checks among those with UEMI was 52% higher compared to those with URMI and RMI because employers often offer annual general health checks as incentives to their staff.[13] However, the role of TC screening as part of regular health checks in explaining the rapid growth of TC in China has not been studied.

Another factor that has been named as a potential factor behind the increase in occurrence of TC in China is iodine intake.[14] China used to be an iodine-deficient country, with a high prevalence of iodine deficiency disorders (IDDs).[15] Since 1996, universal salt iodization was introduced in China as a mandatory policy.[16] With the rapid increase of TC in recent years, its possible role had aroused much public concern.[17,18]

Using two large national databases involving inpatients and commercial critical illness insurance (CII) buyers, we studied the association of the access to screening and salt iodization on the rapid growth of TC. We also estimated the current incidence and the disease burden of TC in China.

What's new?

In recent decades, the incidence of thyroid cancer has increased rapidly worldwide. In China, the role of thyroid cancer screening as part of regular health checks and potential overdiagnosis remain unclear. Moreover, there are concerns among the general public that mandatory salt iodization may have contributed to the epidemic of thyroid cancer. Here, the authors found that the increase in thyroid cancer in China is associated with increased access to health care and screening, but not with salt iodization. Moreover, the results suggest that approximately 1000 individuals are overdiagnosed with thyroid cancer daily, calling for urgent measures to prevent overdiagnosis.

2 | MATERIALS AND METHODS

2.1 | Data sources

Hospital Quality Monitoring System (HQMS) is a mandatory patient-level national database for hospital accreditation under the auspice of the National Health Commission. Since 2013, the Commission has requested Class 3 hospitals in China to submit standardized electronic inpatient discharge records on a daily basis to HQMS in an automated manner. As of December 31, 2017, HQMS covered 31 provinces and 1037 Class 3 hospitals (44.3% of all Class 3 hospitals in China), capturing the medical data of a total of 76 263 617 inpatients. The grade distribution (3A, 3B, 3C, or unclassified) of hospitals in HQMS was similar to that of all Class 3 hospitals in China (Table S1). Class 3 hospitals are the top tier of medical system in China with the minimum requirement of 500 beds. In contrast to tertiary hospitals of western medical system, Class 3 hospitals in China also provide primary and secondary care as well as more specialist service. For each patient in Class 3 hospitals, information on demographic characteristics, clinical and pathological diagnoses, treatment procedures and expenditure breakdowns were extracted from the standardized discharge summary known as the “front-page” of hospital medical records. These records were filed by the doctors in charge of the patients. The diagnoses were then coded based on the International Classification of Diseases-10 (ICD-10) by certified coders in each hospital.

China Reinsurance Company (CRC) is the largest company in China specializing in life insurance business. The CRC database included 93 123 018 commercial CII buyers from 2000 to 2016, accounting for 90% of commercial CII clients in China. Data in the CRC database included demographic characteristics, clinical and pathological diagnoses, type of insurance and insurance claim data of clients.

The level of access to screening was assessed using the type of medical insurances and per capita disposable income (PCDI) as indicators. The three types of social medical insurances (RMI, URMI and UEMI) cover different population groups. Individuals with UEMI generally have a steady job and their employers commonly offer opportunities for annual health checks as a benefit. URMI is the basic social medical insurance for unemployed adults, students, children and the elderly in urban areas. RMI is the basic social medical insurance for those living in rural areas. Data on PCDI, number of inpatients of

Class 3 hospitals and the population of China were extracted from China Statistical Yearbook.[19] Iodine is a necessary element for the synthesis of thyroid hormones and mainly excreted through urine. Median urinary iodine (MUI) has been recommended by international authorities as an indicator of the iodine nutritional status in the population.[20] The MUI values of 31 provinces in China were obtained from national IDD surveys in 1999, 2005 and 2011.[21-23]

The ICD-10 was used to identify patients with TC (code C73).[4,24] In HQMS, the first medical record with the diagnosis of TC (including primary and nonprimary diagnosis) was identified to be a new TC inpatient. Duplicated records of TC patients were excluded in HQMS and CRC. We used the change of the standardized proportion of TC inpatients among all inpatients in HQMS,[25] and the standardized incidence of TC in CII buyers, which were

TABLE 1 Characteristics of TC patients in HQMS and CII buyers

Characteristic	TC patients in HQMS	Total HQMS	TC patients in CII buyers	Total CII buyers
N	512 270	76 263 617	96 181	93 123 018
Gender, N (%)				
Male	120 309 (23.5)	34 378 476 (45.1)	19 490 (20.3)	46 355 364 (49.8)
Female	391 961 (76.5)	41 885 141 (54.9)	76 691 (79.7)	46 767 654 (50.2)
Age				
Mean (SD)	45.6 (12.4)	47.6 (20.5)	44.9 (9.0)	32.1 (21.9)
Median (IQR)	46 (37, 54)	49 (32, 63)	45 (39, 51)	35 (25, 42)
Age distribution, N (%)				
0-19	4423 (0.9)	6 249 963 (8.2)	396 (0.4)	18 143 444 (19.5)
20-44	233 551 (45.6)	25 596 350 (33.6)	46 204 (48.0)	58 427 477 (62.7)
45-64	241 383 (47.1)	27 086 258 (35.5)	49 011 (51.0)	16 532 801 (17.8)
≥65	32 913 (6.4)	17 331 046 (22.7)	568 (0.6)	19 296 (<0.1)
Pathology, N (%)[a]				
PTC	278 406 (97.9)	—	—	—
FTC	2871 (1.0)	—	—	—
MTC	2681 (0.9)	—	—	—
ATC	538 (0.2)	—	—	—

Abbreviations: ATC, anaplastic thyroid cancer; CII, critical illness insurance; FTC, follicular thyroid cancer; HQMS, Hospital Quality Monitoring System; IQR, interquartile range; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; TC, thyroid cancer.

[a]44.5% of pathology data were missing.

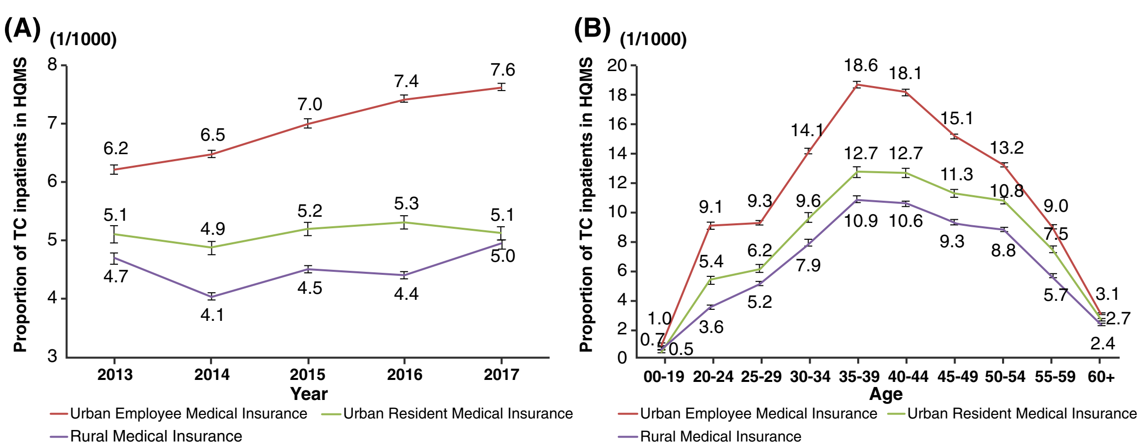

FIGURE 1 The proportion of TC inpatients with different social health insurances. The proportion of TC inpatients with different social health insurances were standardized to the inpatients in HQMS by age and gender. A, The proportion of TC inpatients in HQMS with different social health insurances from 2013 to 2017. B, The proportion of TC inpatients in all HQMS inpatients with three types of social health insurances in different age groups. HQMS, Hospital Quality Monitoring System; TC, thyroid cancer

standardized to the standard population of China in 2016 by age and gender. The number of new TC patients in Class 3 hospitals was calculated by the proportion of new TC patient times the overall number of inpatients of all Class 3 hospitals.[26] The incidence of TC in China was calculated by the number of new TC patients in Class 3 hospitals divided by the total population of China, which was also standardized to the standard population of China in 2016 by age and gender.

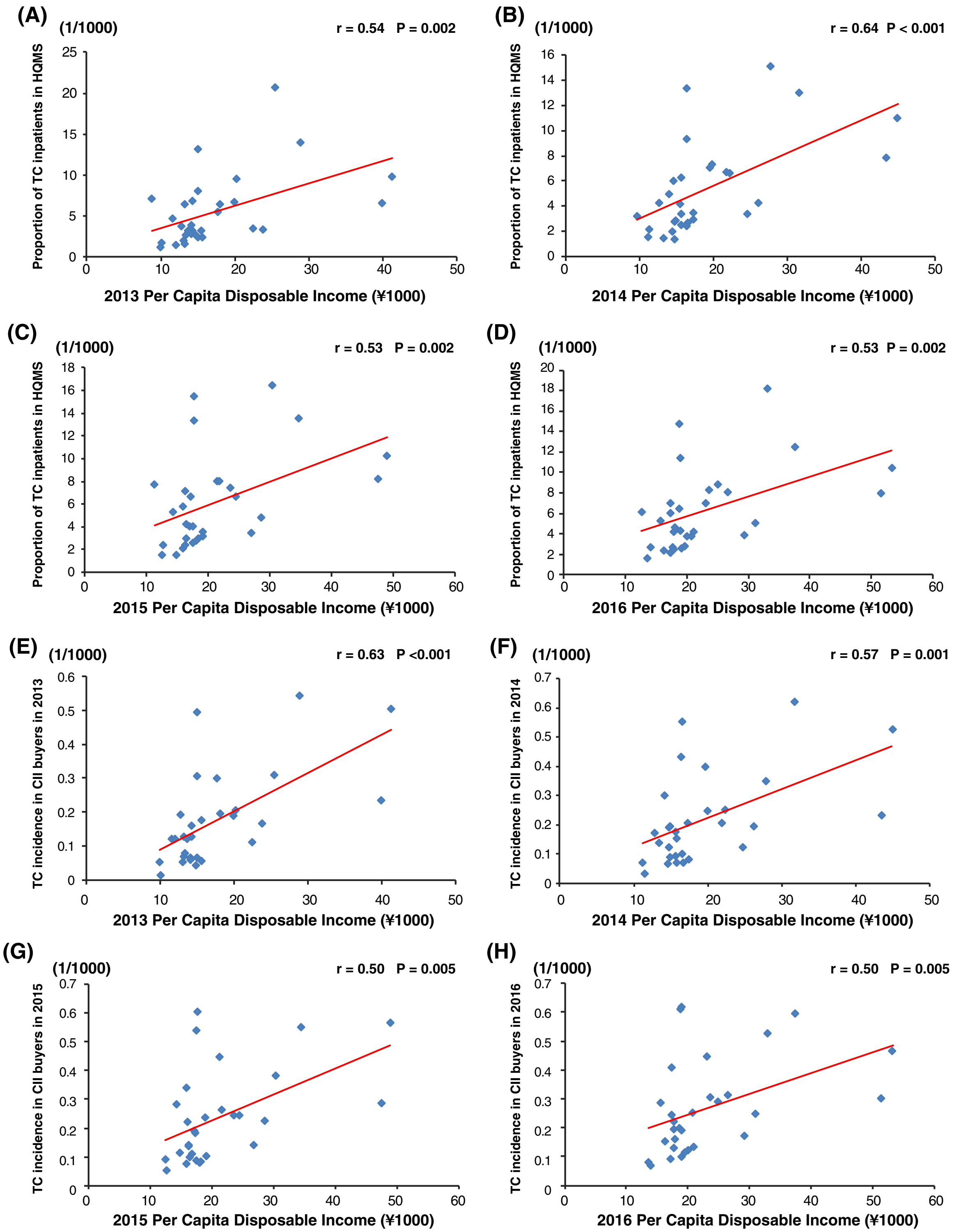

FIGURE 2 The correlation between the occurrence of TC and per capita disposable income. A-D, The relation between per capita disposable income and the proportion of TC inpatients in HQMS at provincial level, for each of the 4 years between 2013 and 2016. E-H, The relation between per capita disposable income and the incidence of TC in CII buyers at provincial level, for each of the 4 years between 2013 and 2016. CII, critical illness insurance; HQMS, Hospital Quality Monitoring System; TC, thyroid cancer [Color figure can be viewed at wileyonlinelibrary.com]

2.2 | Statistical analysis

The incidence of TC in CII buyers had kept increasing since 2000 and increased more rapidly since 2010. We conservatively estimated the number of new TC patients via screening to make our conclusion safer and more convinced. Therefore, we assumed that all the TC patients diagnosed in 2010 were symptomatic and used the incidence of TC in CII buyers as the "background" rate for TC incidence (ie, all the patients were diagnosed after clinical presentations instead of being detected via screening). The overdiagnosed cases of TC were calculated by using the following approach: The number of overdiagnosed TC patients = The number of new TC patients – The number of TC patients with symptoms (the incidence of TC in CII buyers in 2010 * the population of China). We then forecasted the total number of newly diagnosed TC patients in 2019 to 2030 due to screening according to two different predicted trends of changes in rate of diagnosis. The APC was calculated based on the number of new TC patients between 2013 and 2017. Algorithm 1: If the current annual

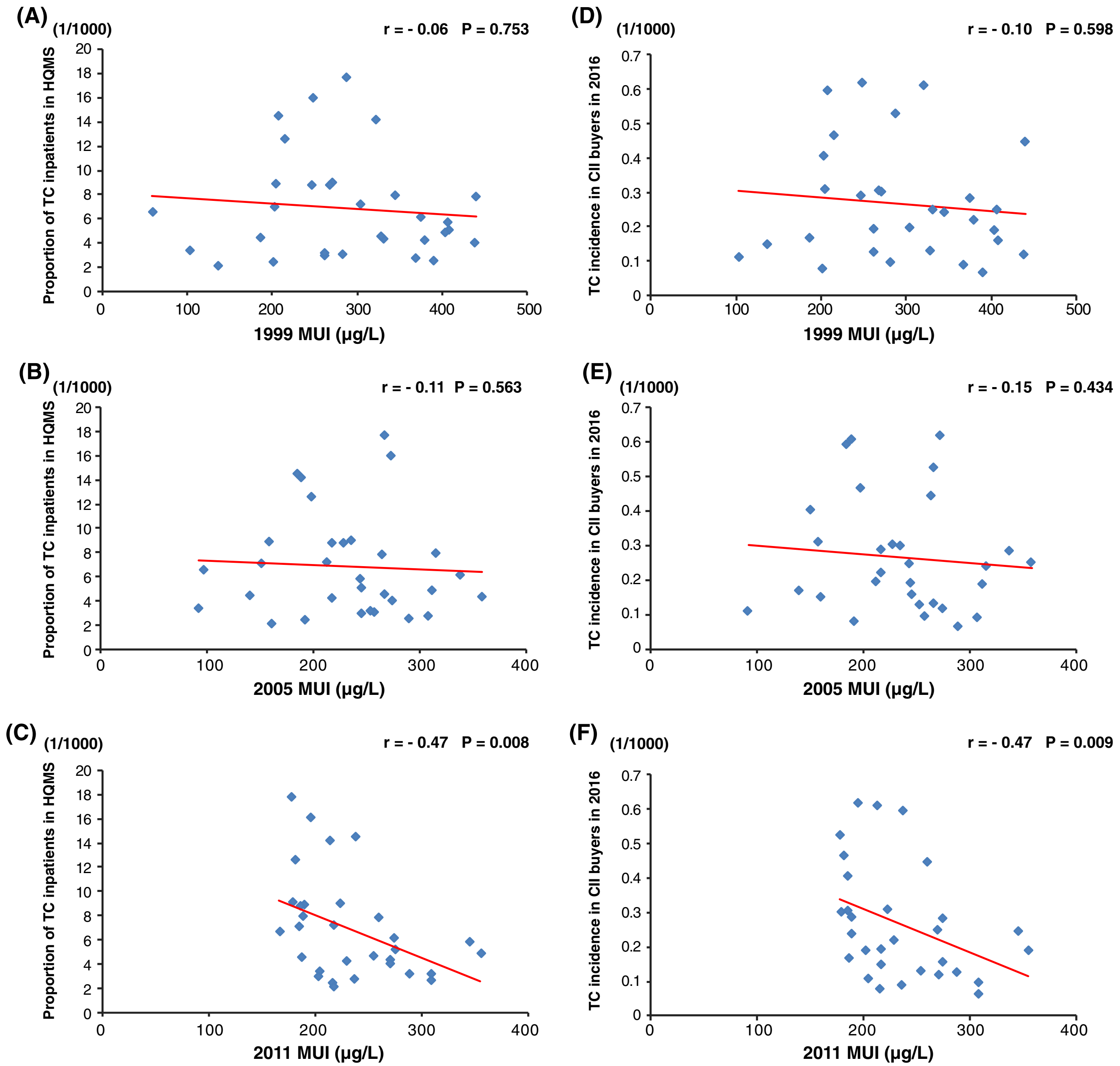

FIGURE 3 The relation between the occurrence of TC and iodine status. The relation between MUI in, A, 1999, B, 2005, C, 2011 and the proportion of TC inpatients in HQMS from 2013 to 2017 at provincial levels. The relation between MUI in, D, 1999, E, 2005, F, 2011 and the incidence of TC in CII buyers in 2016 at provincial levels. CII, critical illness insurance; HQMS, Hospital Quality Monitoring System; MUI, median urinary iodine; TC, thyroid cancer [Color figure can be viewed at wileyonlinelibrary.com]

rate of increase continues, we estimated the incidence of TC in each group 2018 to 2030 using the following approach: Incidence in subsequent year = (Incidence in current year) + (Incidence in current year * APC). Algorithm 2: If the rate of increase gradually slows down followed by a moderate trend of decline, we estimated the incidence of TC in each group using the following approach: 2017 to 2018—same rate of increase as 2013 to 2017; 2018 to 2023—the rate of increase gradually slows down to 0% (by 20% annual decrease according to the APC of 2018); 2023 to 2030—5% annual decrease. The specific APC of each year between 2018 and 2030 by Algorithm 2 was shown in Table S2.

Continuous data were presented as mean ± SD and median (interquartile range [IQR]). Categorical variables were presented as number (percentage) or proportions with 95% confidence interval (CI). CI was calculated using Wald asymptotic confidence limits. The associations between MUI and the proportion of TC inpatients in the HQMS, as well as the incidence of TC in CII buyers were analyzed using Spearman Correlation Coefficient. All *P* values are two-tailed. *P* value <.05 was considered to be significant. All statistical analyses were done with SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

3 | RESULTS

3.1 | General characteristics of the study population

The characteristics of TC patients in HQMS from 2013 to 2017 and in CII buyers from 2000 to 2016 were shown in Table 1. In total, there were 512 270 inpatients with newly diagnosed TC in HQMS. Approximately three quarters of these patients were female. Among the pathological subtypes, papillary thyroid cancer (PTC) was predominant (97.9%). In CRC database, 96 181 TC patients were identified. The proportion of female TC patients was 79.7% in the CRC database.

3.2 | TC and type of social health insurances

Figure 1A showed the proportion of TC inpatients in HQMS with different types of social health insurances from 2013 to 2017. The proportion among those with UEMI increased by 22.7% from 2013 (6.2/1000) to 2017 (7.6/1000). There was a small increase among those with RMI (3.6%) and in those with URMI, the proportion actually dropped (−1.3%). Figure 1B showed the proportion of TC inpatients in all HQMS inpatients with three types of social health insurances in different age groups. The gap between the proportion of TC inpatients in HQMS with different types of social health insurances among those aged 30 to 55 was wider than those aged over 55.

3.3 | The proportion of TC inpatients in HQMS in different provinces and the relationship with income and iodine status

There was a positive correlation between the proportion of TC inpatients in HQMS and PCDI in different provinces in 2013, 2014, 2015, 2016, $P < .01$ (Figure 2A-D). The correlation coefficients were 0.48, 0.59, 0.45 and 0.48, respectively. Likewise, a positive correlation was observed between the incidence of TC in CII buyers and PCDI in different provinces in 2013, 2014, 2015, 2016, $P < .05$ (Figure 2E-H). The correlation coefficients were 0.55, 0.51, 0.44 and 0.37, respectively.

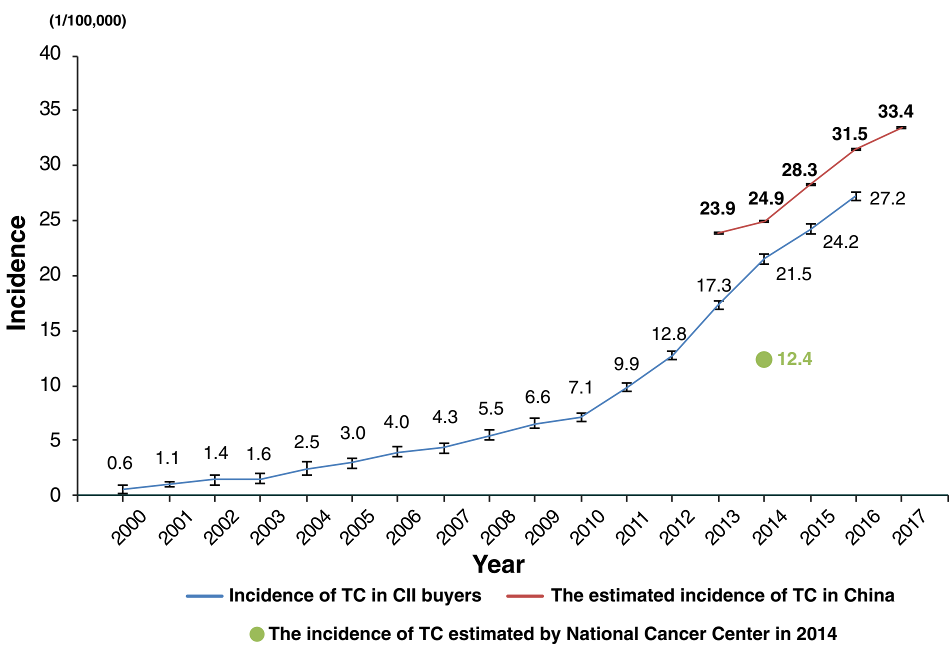

FIGURE 4 The age and gender standardized incidence of TC in China and in CII buyers. The estimated incidence of TC in China and in CII buyers were standardized to the population of China by age and gender. The blue curve was the incidence of TC in CII buyers between 2000 and 2016. The red curve represented the estimated incidence of TC in China between 2013 and 2017 based on the proportion of TC of HQMS and the total number of inpatients of Class 3 hospital. The green dot was the incidence of TC estimated by National Cancer Center of China in 2014 by using data from 449 cancer registries[5]. CII, critical illness insurance; HQMS, Hospital Quality Monitoring System; TC, thyroid cancer

TABLE 2 Burden from hospitalization of patients with TC

Year	2013	2014	2015	2016	2017	2013-2017
Inpatients in HQMS (thousand)	11 982	17 903	19 769	21 963	20 355	76 264[a]
New TC inpatients in HQMS (thousand)	69	95	111	124	113	512
Cost (per admission, ¥)	18 409	19 675	20 876	21 835	21 135	20 611
Average hospital stays (days)	10.1	10.2	10.1	9.9	9.7	10.0
Total inpatients in all Class 3 hospitals (thousand)	54 501	62 910	68 289	76 862	83 960	—
Estimated new TC inpatients in all Class 3 hospitals(thousand)[b]	314	337	394	448	486	1979
Estimated total cost (¥, million)	5774	6638	8228	9778	10 268	40 686
Estimated total hospital stays (thousand days)	3168	3441	3981	4434	4713	19 737

Abbreviations: HQMS, Hospital Quality Monitoring System; TC, thyroid cancer.
[a]The total inpatients in HQMS from 2013 to 2017 excluded medical records of repeated admission.
[b]Assumed that the distribution of Class 3 hospitals included in HQMS were identical to the distribution of all Class 3 hospitals in China, the number of new TC patients in Class 3 hospitals was calculated by the proportion of new TC patients in HQMS times the overall number of inpatients of all Class 3 hospitals.

There was no correlation between the proportion of TC inpatients from 2013 to 2017 and MUI in different provinces in 1999 and 2005, $P > .05$ (Figure 3A,B). There was a negative correlation between the proportion of TC inpatients in HQMS from 2013 to 2017 and MUI in provinces in 2011, with a correlation coefficient of −0.42 ($P < .05$) (Figure 3C). Similar associations were observed in the incidence of TC in CII buyers in 2016 with MUI at provincial levels (Figure 3D-F), as well as in 2012, 2013, 2014 and 2015 (Figures S1-S4).

3.4 | The incidence of TC in China

In CII buyers, the incidence of TC increased from 17.3/100 000 in 2013 to 27.2/100 000 in 2016. Based on the proportion of TC of HQMS and the total number of inpatients of Class 3 hospital,[20] the increase in estimated incidence in China between 2013 and 2017 was 39.7% (23.9/100 000 to 33.4/100 000) (Figure 4). There were 432 635 new TC cases in 2017. Among these new cases, we estimated that 85 154 cases were diagnosed with symptoms and 347 481 cases were overdiagnosed due to screening (Table S3). In 2017, approximately 1000 individuals were overdiagnosed with TC daily.

3.5 | Burden from hospitalization of patients with TC

The burden from TC was shown in Table 2. We estimated that there were 1.98 million newly diagnosed TC inpatients among all Class 3 hospitals in China from 2013 to 2017, responsible for 19.7 million days of hospital stays at an expense of 40.7 billion RMB.

3.6 | The estimated number of TC patients aged 20 to 64 between 2019 and 2030

The number of new TC patients aged 20 to 64 assuming no screening is estimated to be 1.0 million between 2019 and 2030 (Table S3). If the current annual rate of increase continues, the estimated number of newly diagnosed TC patients would be 11.6 million. If the rates of increase gradually slow down followed by a moderate trend of decline, the figure would be 6.1 million. Therefore, without a sharp reduction in screening activities, we forecast that 5.1 million healthy individuals would be overdiagnosed with TC between 2019 and 2030.

4 | DISCUSSION

Using two national databases involving over 76 million inpatients and 93 million commercial CII buyers, our study indicated that the epidemic of TC in China was likely to be the result of increased access to screening, and unlikely to be related with salt iodization. This rapid rise of TC incidence brings a heavy disease burden.

Screening can identify TC which often exists as indolent, subclinical lesions.[27] In our study, TC occurs most frequently in people with UEMI and the rate of increase was highest in this group compared with those with URMI and RMI. A very sharp increase in incidence was also observed in commercial CII buyers. The gap between the proportion of TC inpatients in HQMS with different types of social health insurances became narrowed at age over 55 and disappeared at age over 60, which were the statutory retirement age of female and male employees in China, respectively. That people with UEMI and commercial CII have more access to health checks and screening[13] was likely to be the main reason behind these observations. We also found that income at provincial level was positively related to the proportion of TC inpatients in HQMS in the province. The likely explanation is that people with higher incomes are more likely to be exposed to health checks offered by their employers or paid for out of pocket, similar to what was found in the United States.[7]

There are concerns among the general public in China that the rise in TC may have been the result of salt iodization.[17,18] In our study, iodine status was not associated with TC at provincial level. Since the implementation of salt iodization policy in China, three national urinary iodine sampling surveys were conducted in 1999, 2005 and

2011, and salt iodine concentration was adjusted accordingly. From 1999 to 2011, the trend of MUI in China was decreasing, contrary to the increasing trend of TC incidence.[4] According to the iodine status standards defined by WHO/UNICEF/ICCIDD, most of the provinces in China were in the "adequate" (defined as MUI values 100-199 μg/L) or "more than adequate" (defined as MUI values 200-299 μg/L) iodine intake status. Only four provinces (Jiangsu, Jiangxi, Guizhou and Anhui) were in the "excessive iodine intake status" category (defined as MUI values ≥300 μg/L).[23] Using HQMS data, we found that the occurrence of TC in these four provinces was lower than the national average. In Denmark, the incidence of TC had risen rapidly before national iodine supplementation, and differences in iodine intake did not affect TC incidence.[28] Thus, salt iodination policy is unlikely to be a driver of the rapid increase of TC in China.

'The sharp rise of TC diagnoses brought a heavy burden on medical resources in China. The direct hospitalization expenses from 2013 to 2017 of TC patients in Class 3 hospitals of China was 40.7 billion RMB, which did not include the expenses for long-term treatment and follow-up. In addition, the diagnosis and treatment of TC could seriously impact the quality of life and mental health of the individuals affected.[29,30] Part of the TC patients had to accept permanent thyroxine supplement and suffer from the side effects of TC surgery (hypoparathyroidism, hypocalcemia and vocal cord or fold paralysis).[10]

Our results suggested that previous studies have substantially underestimated the incidence of TC in China. Two recent reports were available from the National Cancer Center of China. The first one estimated the incidence of TC in 2015 at 6.55/100 000 by applying age-specific incidence rates from 72 cancer registries (2009-2011).[4] Another report published in 2018 reported an estimated incidence of 12.40/100 000 in 2014, using data from 339 cancer registries.[5] In our study, we estimated that the number of new thyroid patients among Class 3 hospitals in 2014 was 337 383. The incidence of TC of China was estimated to be 24.9/100 000 for 2014, which were much higher than the incidence published in the previous study.[5]

There is no evidence that screening for TC is effective in reducing TC mortality. There has also been no randomized trial to evaluate the effectiveness of screening.[31] Contrast to the sharp rise of TC incidence, the mortality of TC has remained low and stable in recent decades.[1,3] Roughly 50% of new-diagnosed TC are papillary thyroid microcarcinoma,[27] defined as a PTC ≤1 cm in diameter. The vast majority of these lesions are indolent in nature and do not kill the patients.[10] Identifying these tumors by screening has almost certainly been responsible for the apparent improvement in 5-year relative survival of TC in China and South Korea.[32,33]

Similar to other ecological investigations, our study has limitations. In assessing the relationship between screening and TC diagnosis, we have used the type of medical insurances and PCDI as proxy indicators of level of access to screening in our analyses. We believe however that the much sharper surge in TC occurrence over a short period among the population covered by UEMI compared to those under the other two insurance schemes suggests strongly that a real difference in disease risk of TC between the groups was highly unlikely, and that higher access to screening was a much more plausible explanation. This is also supported by the positive correlation between PCDI and TC occurrence at provincial level. Similarly, there are potential problems of ecological analyses on the iodine question, as provincial MUIs were also used to assess population iodine status and we could not take into account potential confounders. However, it is clear that provinces with up to three to four times higher total iodine exposure than those with lowest exposure have not experienced higher TC occurrence. If anything, there is actually some suggestion that higher urinary iodine might be associated with lower rate of diagnosis of TC. The conclusion that salt iodization was very unlikely to be a factor behind the large rise of TC should therefore be safe.

We concluded that the epidemic of TC in China was associated with the increased access to health check, but not related to salt iodization. The incidence of TC in China was also substantially underestimated. Assuming a gradual slowing down of the rate of increase followed by a moderate trend of decline, there would still be approximately 5.1 million healthy men and women who would become TC patients unnecessarily between 2019 and 2030. As a reference, the estimated 5-year prevalence for all cancers combined in 2011 in China was 7.49 million,[34] and the total number of cancer survivor globally was approximately 32 million in 2012.[35] Previous autopsy series showed that incidental TC lesions were identified in 4.7% to 35.6% of individuals who had no history of TC.[27] Recently, Li et al indicated that large numbers of TC were estimated to be overdiagnosed, including China.[36] The results of this hospital-based study were broadly coherent with the population-based estimates. Therefore, a clear guidance is urgently needed to prevent this vast "reservoir" from being unearthed unnecessarily by uncontrolled screening in China's efforts to achieve the objectives enshrined in *Healthy China 2030*.[37] Our findings may also provide an additional cautionary note to other countries where similar health checks are taking place.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting the results in this article will be made available upon reasonable request to the corresponding authors.

ETHICS STATEMENT

This study was approved by the Research Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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